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(54) Title: METHODS FOR TREATING MIDDLE AND INNER EAR DISORDERS		
(57) Abstract Provided are methods to deliver drugs to the middle or inner ear of a mammal in need of such drug comprising inserting a composition comprising a biocompatible polymer and at least one pharmacologically active agent. More particularly, the invention relates to a method for treating Meniere's disease using a composition of hyaluronic acid and gentamicin.		

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METHODS FOR TREATING MIDDLE AND INNER EAR DISORDERS

FIELD OF THE INVENTION

5 The present invention provides methods for treating middle and inner ear disorders. The methods involve administering a composition comprising hyaluronic acid, or other suitable biocompatible polymer, and at least one pharmacologically active substance useful for treating such disorders.

BACKGROUND OF THE INVENTION

10 To treat various ear disorders, it is often necessary to deliver therapeutic agents to inner and middle ear tissues. A variety of structures have been developed that can deliver/administer therapeutic agents into the external auditory canal of the outer ear including those disclosed in U.S. Pat. Nos. 4,034,759, 3,528,419, 4,159,719 and 2,642,065.

15 However, the delivery of therapeutic agents in a controlled and effective manner to tissue structures of the middle, and particularly, the inner ear (e.g., those portions of the ear contained within the temporal bone which is the most dense bone tissue in the human body) is considerably more difficult. Inner ear tissue structures of primary importance include the cochlea, the endolymphatic sac/duct, the vestibular labyrinth and all of the compartments which include these components. Access to the inner ear tissue regions is typically through a variety of structures including the round window membrane, the oval window/stapes footplate and the annular ligament. For the purposes of this invention, the structures through which access to the inner ear may be accomplished shall be considered middle-inner ear interface tissue structures. In addition, the middle ear is defined as the physiological air-containing tissue zone behind the tympanic membrane (i.e., the ear drum) and ahead of the inner ear. Note also that access to the inner ear may be had through the endolymphatic sac/endolymphatic duct and the otic capsule.

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30 The foregoing inner ear tissues are of minimal size and, in the past, only readily accessible through microsurgical procedures. In order to treat various diseases and conditions associated with these and other inner ear tissues, the delivery of medicines is important. Exemplary medicines, or substances having biological or pharmacological activity, that are typically used to treat inner ear tissues include urea, mannitol, sorbitol,

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glycerol, xylocaine, epinephrine, immunoglobulins, sodium chloride, steroids, heparin, hyaluronidase, aminoglycoside antibiotics (e.g., streptomycin/gentamicin), and other drugs, biological materials, pharmaceutical compositions and therapeutic agents suitable for treating tissues of the human body.

5 The effectiveness of therapies for the middle and inner ears is hampered by the routes of administration currently available. For example, typically antibiotics are systemically administered to treat infections of the middle ear. Systemic administration of antibiotics to combat middle ear infection generally results in a prolonged lag time to achieve therapeutic levels in the middle ear, and requires high initial doses in order to
10 achieve such levels. These drawbacks complicate the ability to obtain therapeutic levels and may preclude the use of some antibiotics altogether. Systemic administration is most often effective when the infection has reached advanced stages, but at this point permanent damage may already have been done to the middle ear and inner ear structure.

15 Drugs also can be administered by injection or lavage to the middle ear, but such administration cannot generally be used to achieve prolonged therapeutic levels. Similarly, ear drops can be used to apply antibiotics to the ear canal, but the ability of antibiotics to reach the middle ear when applied in this manner is difficult to predict or control, and poses difficulties, e.g., regarding the possible ototoxic effects of
20 penetration enhancers that may be used. Middle ear drug delivery is further complicated by the fact that the ciliary action of the cells lining the mucous membrane clears the middle ear of medications that do arrive.

 Delivery of drugs to the inner ear is even more problematical. For example, in the case of Meniere's disease, patients with a unilateral functional lesion at the level of
25 the vestibular labyrinth component of the inner ear experience intense episodes of vertigo, usually with nausea and vomiting. They may also experience continuous disorientation in space. All of these symptoms can be incapacitating. Meniere's disease is caused by a variety of histopathological states, all of which can be termed vestibulopathies. The current primary therapy for Meniere's patients, if change in diet
30 and administration of antibiotics does not alleviate the symptoms, is a vestibular nerve

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section. By sectioning the vestibular nerve, vestibular function is irreversibly lost on one side and allows the patient to reorient over a period of time. The success rate is high, yet significant risks are involved. This is a major intracranial operation with hospital stays averaging five days. Even though the procedure is straightforward, it presents the risk of intracranial infection, cerebrospinal fluid (CSF) leak, and complications due to general anaesthetics. In addition, there is severe postoperative vertigo for two to three days.

An alternative therapy is to inhibit vestibular function with an ototoxic therapeutic agent. Aminoglycoside antibiotics, such as gentamicin sulfate (GS), are known to be ototoxic, causing loss of hearing and vestibular function. However, with the appropriate dose, it should be possible to inhibit vestibular function without affecting hearing. If the drug is placed in the middle ear, which is accessible from the outside, the drug can diffuse through the round membrane and into the inner ear, which is very difficult to access. It is essential that drug remain in contact with the round membrane for all of the dose to be delivered.

Clinical studies for treating Meniere's disease have been performed using GS, with some success. (See, e.g., Nedzelski, J.M., et al., "Treatment of Meniere's Disease with Topical Gentamicin: A Preliminary Report," J. Otolaryngology, Vol. 21, pp. 95-101 (1992) and Paines, L.S. and Duneen, R., "Irritative Spontaneous Nystagmus Following Intratympanic Gentamicin for Meniere's Disease," Laryngoscope, Vol. 103, pp. 745-49 (1993).) However, these studies used GS solutions, which do not reliably remain in the middle ear, either due to leakage around the eardrum or via percolation back through the eardrum, if administered intertympanically. These problems lead to variation in dose, often requiring additional treatments, which increase the chance of hearing loss. Consequently, GS treatment to treat Meniere's disease has met with limited acceptance. Development of a dosage form which could reliably deliver a fixed dose and remain in contact with the round membrane would be highly advantageous for solving this and other problems relating to delivering drugs to the middle and inner ears.

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Clearly what is needed is a method to deliver therapeutically effective levels of drug to sufferers of diseases and other conditions of the middle or inner ear, in a fashion that is prompt, responsive, prolonged, effective, and safe.

SUMMARY OF THE INVENTION

5 The present invention provides a composition incorporating one or more pharmacologically active agents, the composition being particularly useful in a method for treating middle or inner ear diseases and other conditions capable of being treated by such an agent. The composition comprises a biocompatible polymer support incorporating a therapeutically effective releasable amount of at least one such active agent, the characteristics of the composition being such that, upon insertion into the
10 middle ear, the composition is capable of maintaining its position in order to provide a surface that substantially contacts the round membrane of the middle ear and providing extended release of active agent to the inner ear. Preferably, the biocompatible polymer is biodegradable as well.

15 More specifically, the present invention provides a gel composition system and methods for delivering a drug or other therapeutic, e.g., GS, to the middle or inner ear in a more controlled fashion. The GS is administered in an amount of about 5-360 mg per patient, more specifically about 20 to 200 mg per patient and, even more specifically, about 40 mg per patient. If the doses are greater than 200 mg, the patient
20 should be dosed more than once. Those skilled in the art can determine optimal doses and dosage schedules.

 The gel component of the system may comprise hyaluronic acid. Hyaluronic acid ("HA") is a well known, naturally occurring polysaccharide containing alternating N-acetyl-D-glucosamine and D-gluconic acid. The term "hyaluronan" is sometimes
25 used interchangeably. As used herein, HA is intended to mean hyaluronic acid, salts thereof such as the sodium salt, and chemically modified derivatives of hyaluronic acid such as "hylan." Hylan is a cross-linked, but soluble derivative of HA whose preparation is described in detail in U.S. Pat. No. 4,713,448. Many other forms of HA are also known including those set forth in U.S. Pat. Nos. 5,128,326 and 5,442,053, the
30 disclosures of which are incorporated by reference. The terms "hyaluronic acid" and

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"HA" are meant to be broadly inclusive of all forms of hyaluronic acid-related molecules, including those referred to above. HA usually occurs as the sodium salt. The molecular weight of HA is generally within the range of 50,000 to 8×10^6 or higher.

5 HA is one of the major components of the extracellular matrix and is found in abundance in tissues like synovial fluid and the vitreous of the eye. HA and its salts give very viscous and elastic solutions in water or physiological salt solution.

HA does not produce a foreign body reaction when implanted into a living organism and has an excellent biocompatibility. It is also biodegradable. The combination of these properties together with the known viscoelasticity of HA facilitates the use of HA in the biomedical field. Thus, a 1% solution of sodium hyaluronate (Healon™) is used in eye viscosurgery (L. A. Pape and E. A. Balazs, Ophthalmology, 87, No. 7, 1980). HA also is used to impart biocompatibility to various polymeric materials. (E. A. Balazs and A. Leshchiner, U.S. Pat. No. 4,500,676, 15 1985).

The preferred composition comprises a gel which is a commercial preparation of sodium hyaluronic acid called Healon™. Healon™ is an HA preparation with a molecular weight of about three million. It can be purchased from Pharmacia. Healon™ can be impregnated with high doses of GS (equivalent to loads of up to 200 mg/ml of gentamicin base, corresponding to 314 mg/ml of GS). The gel can be injected behind the eardrum under local anaesthetic. The preferred method for injection is with a needle. However, other methods, for example, a pumping device with a small orifice, may also be used.

The composition is fluid enough to be injected through a fine gauge needle (as small as 26 gauge), assuring proper placement of the gel, but viscous enough that it will remain in contact with the tissue for an extended period of time. Finally, the Healon™ is biodegradable. After a period of time, the gel decomposes to biocompatible materials and disappears from the site of administration. In the laboratory, the gel appears to be liquid enough to disappear from the site within seven to ten days with minimal agitation. Consequently, the GS/sodium hyaluronic acid composition may 30

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provide a superior dosage form for nonsurgical treatment for unilateral vestibular dysfunction and other disorders of the middle and inner ears.

The drug delivery composition may include the following:

1. HA solutions in which a drug substance is dissolved or dispersed;
- 5 2. A cross-linked HA gel forming a macromolecular "cage" in which a drug substance is dispersed so long as cross-linking does not make the polymer rigid;
3. A cross-linked mixed gel of HA and at least one other hydrophilic polymer in which a drug substance is dispersed;
4. A cross-linked gel of HA or cross-linked mixed gel of HA and at least
10 one other hydrophilic polymer containing a drug substance which is covalently attached to the macromolecules of HA or the other polymer.

Such compositions are set forth in U.S. Pat. No. 5,108,326, which is incorporated herein by reference. However, they are not disclosed for use in treating middle and inner ear disorders. Any substance which has biological or
15 pharmacological activity and which is normally considered to be a drug or other therapeutic can be used as the drug component in the composition according to the present invention. Exemplary substances are set forth above. The terms "drug" and "drug substance" are also used herein to describe such substances. The substances can be soluble or not soluble in aqueous medium; they can be of relatively low molecular
20 weight or a polymeric substance, and the choice of the substance will clearly depend upon the specific use of the end product and disease or other problem to be treated. It should be understood that any combination of one or more such substances can be used in the products and methods according to the invention.

As mentioned above, HA is the preferred polymeric component of the
25 composition which controls release of the drug. Other biocompatible polymers may also be used including celluloses, gelatins, Pluronic, Tetronics, the latter two being poly (ethylene oxide)/poly (propylene oxide) materials. Other materials that may be used in place of HA include the chondroitin sulfates and the general class of mucopolysaccharides (e.g., glycosaminoglycans) and other biocompatible polymers
30 having characteristics similar to HA.

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When a drug substance is dissolved or dispersed in the biocompatible polymer, its diffusion is substantially slower than when in solution and this contributes to the delivering properties of the system. Without being bound by theory, in the case of a drug containing cationic groups, an ionic interaction can occur between HA
5 macromolecules having carboxyl groups and the drug and this interaction slows down the diffusion of the drug from the system even further.

The HA concentration in the products, based on the soluble polymers, can be in the range of from about 0.05 to 4% by wt. and higher, depending on the end use of the product. The drug concentration can be varied over very broad limits and preferably
10 should be chosen depending upon the solubility of the drug, its pharmacological activity, the desirable effect of the end product, patient size, weight and so forth, all factors known to those skilled in the art. Although many of the above-discussed medicines can already be used as injectables, the products according to the invention containing non-soluble HA are substantially more efficient as injectable drug delivery
15 systems for use in methods of treating the middle and inner ears.

In a further aspect of the present invention, the pharmacologically active agent may be present in the form of a hydrophobic ion pair complex with an amphiphilic material. Incorporation of the pharmacologically active agent in a hydrophobic ion pair complex is particularly useful for slowing the rate of release of the pharmacologically
20 active agent, when a slower release rate is desired. Preferred amphiphilic materials for forming a hydrophobic ion pair with gentamicin are sodium dodecyl sulfate (SDS) and bis-(2-ethylhexyl) sodium sulfosuccinate (AOT). The hydrophobic ion pair complex may be prepared according to procedures known in the art. Additional information concerning hydrophobic ion pair complexes and their preparation may be found in PCT
25 Publication No. WO 94/08599, published April 28, 1994, and pending U.S. Patent Application Serial No. 08/473,008, filed June 6, 1995, the contents of both of which are incorporated herein in their entireties.

For treating Meniere's disease, the preferred pharmacological agent is gentamicin sulfate. Other ototoxic agents may also be used, including aminoglycosides
30 and other agents, including acetylsalicylic acid, amikacin, aminoglycosides,

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chloramphenicol, chlorhexidine, chloroquine, cytostatics, dantrolene, deferoxamine, doxycycline, erythromycin, furosemide, gentamicin, kanamycin, minocycline, naproxen, neomycin, piroxicam, propylene glycol, spinal anesthesia, bupivacaine and streptomycin.

5 Other diseases of the middle and inner ear may also be treated using the methods and products of the invention, including any vestibular dysfunctions, local infections (viral or bacterial) and reduced hearing caused by diminished blood flow.

Another aspect of the present invention includes the use of a combination of materials in the manufacture of a medicament composition for treatment of a disease of
10 the inner ear or middle ear when transplanted in the middle ear, characterized in that the combination of materials includes a biocompatible polymer and a substance having biological or pharmacological activity. In a further aspect, the present invention includes a method of transplanting the composition into the middle ear comprising placing within the middle ear the composition having the biocompatible polymer and
15 the substance having biological or pharmacological activity.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Materials. Gentamicin sulfate (GS), USP, is obtained from Paddock. Sodium hyaluronate gels (Healon™) are commercially available from Pharmacia. The sodium HA has an initial concentration of 14 mg/ml. Concentrations of gentamicin are given in
20 terms of GS. This corresponds to a gentamicin base concentration that is 0.63 times the concentration of GS.

The Healon™/GS preparations are formed by mixing equal volumes of Healon™ (14 mg/ml) and a concentrated solution of GS dissolved in phosphate-buffered saline (PBS). Healon™ and GS were mixed manually by repeatedly drawing
25 the solution into and out of a syringe through an 18-ga. needle for a minimum of five minutes. Other methods including vortexing or stirring with a stir plate and stir bar were found to be ineffective due to viscosity of the Healon™. For most studies, the final GS concentration in the composition is 314 mg/ml (i.e., 200 mg/ml of gentamicin base).

Release Studies. Composition samples are incubated at 37°C in a water bath unless otherwise noted. Release studies are measured as cumulative release, with the entire receiver volume replaced with fresh PBS at the various time points. Amounts are given as the percentage of the total dose of GS. For a typical release study, the loading factor is 200 mg of gentamicin base per 1 ml of gel. 0.2 ml of gel is placed into 0.8 ml of receiver fluid. The receiver volume for all of the in vitro release studies is 0.8 ml, but the kinetics do not change if the receiver volume is doubled. Therefore, the total dose is 64 mg of GS, which has been found to be effective for inhibition of vestibular function. The remaining sodium hyaluronate completely dissolves within seven to ten days, depending on the extent of agitation, suggesting biodegradation should be rapid.

Analysis. Determination of gentamicin levels in the release medium, either PBS or CSF, is performed on an Abbott TDx clinical analyzer. Calibration standards are run each time a new reagent kit is used on the analyzer. In addition, three controls are run with each individual analysis performed to ensure accuracy. Gentamicin levels are measured by derivitization with o-phthaldehyde (OPA) following Sampath and Robinson's 1990 procedure (Sampath, S.S., Robinson, D.H. "Comparison of new and existing spectrophotometric methods for the analysis of tobramycin and other aminoglycosides." *J. Pharm Sci.* 79 (1990) 428-431) with modifications employed by Goosen *et al.* (Zhang, X., Wyss, U.P., Pichora, D., Goosen, M.F.A. "Biodegradable controlled antibiotic release devices for osteomyelitis: optimization of release properties." *J. Pharm. Pharmacol.* 46 (1994) 718-724.) The two methods are in excellent agreement (see below).

The target dose for these studies is taken to be approximately 64 mg of GS. As the volume of the middle ear is limited, and to allow the administration of the drug to be as convenient as possible, the total dose is loaded into 0.2 ml of sodium hyaluronate gel. The middle ear accommodates volumes up to 0.8 ml.

Example 1 - Control Release Studies. Initial release studies are performed into PBS, a common receiver fluid for controlled release studies. The release kinetics are well controlled and reproducible over the first four hours. There appears to be a small burst effect from drug adsorbed to the surface of the gel, but it is much less than

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normally seen with other biodegradable polymers. Steady-state release is rapidly established. By four hours, much of the drug is released (50-60%), and the rate of release begins to slow. The drug is nearly completely delivered (~75%) by 24 hours. The variability is very small, with a relative standard deviation of 2-4% from run to run.

5 As an approximation to the environment of the middle ear, release is next measured into CSF. The kinetic profile is approximately the same as in PBS, except that the amount of drug released in a given time is slightly lower (~90% of the level for release into PBS at a given time point). At four hours, the amount released is closer to 50% rather than 60%. However, by 24 hours, the total amount released is
10 approximately 80-90%. The correlation between release into PBS and CSF is very high ($r^2 = 0.999$). It appears the presence of serum components leads to small diminution in the release from the gel, but does not significantly change the kinetics or limit its utility.

 To determine the nature of the controlled release properties of this system, the
15 rate of initial release is examined carefully. Monitoring the release rate over the first half-hour, steady-state occurs within ten minutes. From that time until the system is nearly depleted of GS, the amount of GS released is linear with the square root of time. Also, the composition displays very little burst effect, even at 200 mg/ml, indicating that very little of the drug is adsorbed to the surface of the gel.

20 Comparison of the data to the previous release profiles indicates that the rate of release is much faster as the system is sampled more often. The composition is always somewhat fluid, unlike solid implants or microspheres or other controlled release dosage forms. This mobility means that agitation of the gel surface will be more disruptive than in those solid preparations, leading to increased rates of release. In
25 addition, all of the release studies are cumulative determinations, meaning receiver fluid is replaced by fresh solution. This has the effect of increasing the concentration gradient that existed just prior to sampling. The more frequently this is done, the faster the release rate. In order to probe the effects of agitation and fluid replacement, another sampling technique is employed, using a microliter syringe to remove 10 μ of sample.

Comparison of the release profile shows that this sampling method does not lead to rapid GS release over the first thirty minutes.

Example 2 - Effects of Loading Factor. The release of GS from HA is measured for loading factors of 50, 100 and 200 mg/ml. The cumulative percent release into PBS is more rapid for the lower loading factor. However, the total flux decreases with loading factor, as would be expected for diffusion-limited delivery systems. Both preparations display linear release kinetics over the one to four hour time frame.

Example 3 - Comparison of Methods for Quantitation of GS. Two different methods are used to quantitate GS release from the HA gel: (1) spectrophotometric determination of GS following chemical modification with OPA and (2) an automated clinical chemistry method using antibody binding and fluorescence detection. The instrument is called TDx (Abbott Laboratories). Both of these methods are well established for their ability to measure GS at microgram per milliliter concentrations. Both exhibited linearity across the concentration range used in these studies. All samples are diluted 500-1000-fold before being assayed.

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We claim:

1. A method for delivering a medicine to the inner ear of a mammal in need of such medicine comprising inserting into the middle ear a composition comprising a biocompatible polymer and at least one substance having biological or pharmacological activity.
2. A method according to Claim 1, wherein said biocompatible polymer is hyaluronic acid.
3. A method according to Claim 1, wherein said substance having biological or pharmacological activity is an aminoglycoside antibiotic.
4. A method according to Claim 3, wherein said substance having biological or pharmacological activity is gentamicin or gentamicin sulfate.
5. A method according to Claim 1, wherein said biocompatible polymer is hyaluronic acid and said substance having biological or pharmacological activity is gentamicin or gentamicin sulfate.
6. A method according to Claim 2, wherein said hyaluronic acid is Healon.TM
7. A method according to Claim 4, wherein said substance having biological or pharmacological activity is gentamicin sulfate.
8. A method according to Claim 5, wherein said substance having biological or pharmacological activity is gentamicin sulfate and said hyaluronic acid is Healon.TM
9. The method according to Claim 1, wherein the substance having biological or pharmacological activity is in the form of a hydrophobic ion pair complex with an amphiphilic material.
10. The method according to Claim 9, wherein the amphiphilic material comprises at least one of sodium dodecyl sulfate (SDS) and bis-(2-ethylhexyl) sodium sulfosuccinate (AOT).
11. Use of a combination of materials in the manufacture of a medicament composition for treatment of a disease of the inner or middle ear when transplanted in the middle ear, characterized in that the combination of materials includes a

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biocompatible polymer and at least one substance having biological or pharmacological activity.

12. The use of the combination of materials as recited in Claim 11, wherein the biocompatible polymer is hyaluronic acid.

5 13. The use of the combination of materials as recited in Claim 11, wherein the substance having biological or pharmacological activity is an aminoglycoside antibiotic.

14. The use of the combination of materials as recited in Claim 11, wherein the substance having biological or pharmacological activity is gentamicin or gentamicin sulfate.

10 15. The use of the combination of materials as recited in Claim 11, wherein the biocompatible polymer is Healon.TM

16. The use of the combination of materials as recited in Claim 11, wherein the substance having biological or pharmacological activity is in the form of a hydrophobic ion pair complex with an amphiphilic material.

15 17. The use of the combination of materials as recited in Claim 16, wherein the amphiphilic material comprises at least one of sodium dodecyl sulfate (SDS) and bis-(2-ethylhexyl) sodium sulfosuccinate (AOT).

18. The use of the combination of materials as recited in Claim 11, wherein the disease of the middle or inner ear is a vestibular dysfunction disease.

20 19. The use of the combination of materials as recited in Claim 11, wherein the disease of the middle or inner ear is Meniere's disease.

20. The use of the combination of materials as recited in Claim 11, wherein the disease of the middle or inner ear is a localized viral or bacterial infection.

25 21. The use of the combination of materials as recited in Claim 11, wherein the disease of the middle or inner ear includes a loss of hearing caused by diminished blood flow.

22. A method of transplanting a composition into the middle ear comprising placing within the middle ear a composition characterized as having a biocompatible polymer and at least one substance having biological or pharmacological activity.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,442,053 A (DELLA VALLE ET AL.) 15 August 1995, see the entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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